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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/505,314	04/11/2005	Sakayu Shimizu	21147 (C038435/0178882)	2382

7590 01/26/2006
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New York, NY 10104-3300

EXAMINER

MEAH, MOHAMMAD Y

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 01/26/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/505,314

Applicant(s)

SHIMIZU ET AL.

Examiner

Mohammad Meah

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 7th November, 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 1-9 and 19 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 10-17, 20 and 21 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 8/20/04
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

The applicant, on date 11/07/2005 elected group II (claims 10-17 and 20-21) for examination and claims 1-9 and 19 are withdrawn from consideration.

Election/Restriction

The applicant, on date 11/07/2005 elected with traverse Group II (claims 10-17 and 20-21) drawn process of producing levodione by transformed microorganism expressing NADPH dehydrogenase enzyme for examination.

Applicant's election of group II in the reply filed on 11/07/2005 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Therefore Group I (claims 1-9 and 19) of election/restriction-office action of date 10/12/2005 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected Groups.

Priority

Acknowledgement is made of applicant's claimed priority date based on application filing date of 02/15/2003 of PCT/EP03/01537 and foreign priority on application filing date of 02/22/2002 of European patent office EP0 02003968.

Claim Rejections

The following is a quotation of the first paragraph of 35 U.S.C. 112:

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The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-14, 16-17 and 20-21 are rejected under U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor at the time the application was filed, had possession of the claimed invention.

These claims are directed to methods of producing levodione from ketoisophorone comprising transformed microorganism expressing any NADPH dehydrogenase (claims 10-11, 13-14, 16-17 and 21) or any old yellow enzyme (OYE, claims 12 and 20). The specification fails to describe in any fashion the physical and/or chemical properties of the nucleic acid encoding NADPH dehydrogenase or old yellow enzyme necessary for said methods. Given this lack of description of representative species encompassed by the genus of the claim, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Claims 10-14, 16-17 and 20-21 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of producing levodione from ketoisophorone comprising transformed microorganism expressing the *S. cerevisiae* oye encoded by oye2 or oye3 gene does not reasonably provide

enablement for methods of producing levodione from ketoisophorone comprising transformed microorganism expressing any NADPH dehydrogenase or any old yellow enzyme. The claims broadly recite the methods of producing levodione from ketoisophorone comprising transformed microorganism expressing **any** NADPH dehydrogenase or any old yellow enzyme. The specification fails to describe how any microorganism expressing **any** NADPH dehydrogenase can produce levodione from ketoisophorone and fails to teach how to make nucleic acids encoding any NADPH dehydrogenase or any old yellow enzyme as needed to practice the scope of the claimed methods.

Claims 10-11, 13-14 and 16-17 and 21 are so broad as to include methods of producing levodione from ketoisophorone comprising transformed microorganism expressing **any** NADPH dehydrogenase, while claims 12 and 20 are so broad as to include methods of producing levodione from ketoisophorone comprising transformed microorganism expressing **any** old yellow enzyme. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number transformed microorganisms expressing **any** NADPH dehydrogenase or old yellow enzyme broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the

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ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of two NADPH dehydrogenases. While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass methods of producing levodione from ketoisophorone comprising transformed microorganism expressing **any** NADPH dehydrogenase or old yellow enzyme because the specification does not establish: (A) regions of the protein structure which may be modified without effecting NADPH dehydrogenase activity; (B) the general tolerance of NADPH dehydrogenase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any NADPH dehydrogenase residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

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Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any method of producing levodione from ketoisophorone comprising transformed microorganism expressing **any** NADPH dehydrogenase or old yellow enzyme. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of NADPH dehydrogenase genes or old yellow enzyme genes, having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

CLAIM Rejection - 35 U.S.C 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless

e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 10-12, 13-14, 16-17 are rejected under 35 U.S.C. 102(b) as being anticipated by Fukuoka et al. (EP1074630). Fukuoka et al. teach the use of immobilized microorganisms (yeast including *Saccharomyces cerevisiae*) to convert ketoisophorone to levodione at pH 4.5- 8.5 and temperature 25-60⁰ C. While the yeast disclosed by

Fukuoka et al. are not disclosed as "transformed" microorganisms each of these yeast clearly express one or more NADPH dehydrogenases inherently and thus read on the instant claims. Furthermore the *S cerevisiae* disclosed inherently express old yellow enzyme and thus claim 12 is anticipated as well.

Claims 10, 12-13, 16-17, 20 are rejected under 35 U.S.C. 102(a) as being anticipated by Kataoka et al. (Biosci.biotech. biochem. 2002, 66, pp 2651-2657). Kataoka isolated OYEs (OYE-2 and OYE-3) from *canida macedonieniesis* and stated (page 2653) that *canida macedonieniesis* converts ketoisophorone to levodione at pH 4.5- 8.5 and temperature 25-60⁰ C. While the *canida macedonieniesis* disclosed by Kataoka et al. are not disclosed as "transformed" microorganisms, *canida macedonieniesis* clearly express one or more NADPH dehydrogenases inherently and thus read on the instant claims. Furthermore the *canida macedonieniesis* disclosed inherently express old yellow enzymes (OYE-2 and OYE-3) and thus claims 12-13 are anticipated as well.

CLAIM Rejection - 35 U.S.C 103a

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

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to a person having ordinary skill in the art to which said subject matter pertains.

Patentability shall not be negated by the manner in which the invention was made.

Claims 10-17 and 20-21 are rejected under 35 U.S.C. 103(a) by Vaz et al. (Biochem. 1995, 34, 4246-4256) in view of Fukuoka (EP1074630) and Niino et al. (JBC 1995, 270, 1983-1991).

Vaz et al. (Biochem. 1995, 34, 4246-4256) teach the use of old yellow enzymes (NADPH dehydrogenase) from yeast (*S. carisbergensis*) or OYEs (including oye2 and oye3) from *S. cerevisiae* for the reduction of olefinic bond (ketoisophorone to levedione).

Niino et al. (JBC 1995, 270 1983-1991) teach genes of OYEs (OYE-2 and OYE-3) from *S. cerevisiae* and transformed *E. coli* expressing these genes.

Fukuoka et al. teach the use of immobilized microorganisms (yeast, including *Saccharomyces cerevisiae*) to convert ketoisophorone to levodione at pH 4.5- 8.5 and temperature 25-60⁰ C.

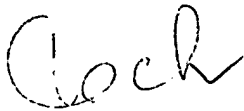
As such it would have been obvious to one of ordinary skill in the art to use transformed microorganisms taught by Niino et al., which express the OYEs shown by Vaz et al. to catalyze the conversion of ketoisophorone to levodione, to convert ketoisophorone to levodione at pH 4.5- 8.5 and temperature 25-60⁰ C as taught by Fukuoka et al.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mohammad Meah whose telephone number is 571-272-1261. The examiner can normally be reached on 8:30-5PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



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